PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for the randomized controlled trial: Treatment of early IUGR with low molecular weight heparin (TRACIP)
AUTHORS	Mazarico, Edurne Peguero, Anna Camprubí, Marta Rovira, Carlota Gomez Roig, MD Oros, Daniel Ibañez, Patricia Schoorlemmer, Jon Masoller, Narcís Tàssies, M Dolors Figueras, Francesc

VERSION 1 - REVIEW

REVIEWER	David Petroff
REVIEW RETURNED	25-Nov-2017

GENERAL COMMENTS	Mazarico and colleagues present the trial protocol for their upcoming randomized controlled triple blinded study on the effectiveness of low molecular weight heparin in the treatment of early IUGR. As referee of a trial protocol article, I see it as my duty to ensure primarily that the trial itself is described with sufficient completeness, clarity and accuracy. In this regard, I feel the authors have done a commendable job, meaning the article could be published as is. Nonetheless, the trial itself could perhaps benefit from some reworking and the description of it as well. Here are some concrete suggestions and points to consider. General Comments 1. Primary outcome: please specify how the primary outcome is defined in the case of pregnancy loss, how will other missing data be treated 2. I do not understand how the log-rank test of the primary objective will provide a meaningful additional analysis. The problem of pregnancy loss remains, though other causes of missing data may be treated as censored. The length of time from inclusion to delivery is not really a direct quantity of interest, it merely correlates very strongly with gestational age at birth. 3. The power analysis contends that a “clinically relevant difference” in gestational age at delivery is 1 week although an earlier argument demonstrates that relevance depends strongly on current gestational week (“between 24 and 28 weeks, each week…increases survival without sequelae by 10-15%; and between 28 and 32 weeks…by 5%). Please provide the exact numbers for gestational age at birth from the “4 studies” in the meta-analysis, not just the differences.

	4. It may not be possible to blind some personnel and patients effectively because of bruising. Please address this issue and perhaps collect data on blinding success within the trial. 5. The primary outcome is not based on identical descriptions of methods between the registered trial ("caudal skull length") and here ("crown rump length"). Please change the registered version accordingly. 6. A CONSORT checklist was provided, but in this context, I think a SPIRIT checklist would make more sense. Specific comments 1. Abstract: The introduction is a little too long whereas the "Methods and Analysis" section presents nothing about the analysis. Please include information on the mathematical techniques to be used, treatment of missing data, etc. 2. The section on "biological plausibility" is rather long compared to other parts of the manuscript. 3. The section on "clinical evidence" is too one-sided for my taste. For one thing, the results of a large individual patients data meta-analysis (Rodger et al., Lancet, 2016; 388: 2629–41) should be included, which included SGA as an outcome (Table 4) and the subgroup of women with previous SGA for a combined outcome (Table 5). For another, the statement that "these studies only include pregnant women at risk" seems to strong considering the studies from Yu et al quoted later (citations 19, 20) that do include many women with IUGR and have sample sizes larger than those planned here. 4. The English is quite good, but should be looked over in some spots, e.g. a. "endorsed" in Abstract b. Typo "anlysis" in Abstract c. "0.5% of pregnancies…has been shown to be effective" in Strengths and Limitations d. "is only a surrogate" in Strengths and Limitations e. "depends on the correct interaction" in Introduction f. Lines 36-38 on page 5 "Fetal cytotrophoblast…spiral arteries" g. Typo "discreet" as 6th control variable h. "…allocation group from a web-based system" in ALLOCATION i. "Patients will be informed that their participation…as their clinical documentation" (plural not singular) in ETHICS AND DISSEMINATION j. "The trial has been entered in the public registry" in in ETHICS AND DISSEMINATION

REVIEWER	dr. C.N.H. Abheiden
REVIEW RETURNED	26-Nov-2017

GENERAL COMMENTS	The authors present a protocol for a randomized controlled trial (RCT) in which they investigate the influence of low-molecular-weight heparin (LMWH) in women with a fetus with intra-uterine growth restriction. Their primary outcome is prolongation of gestational age. There are several remarks I would like to make. - It is a triple blind RCT and women are randomized to receive either LMWH or a placebo. All large trial investigating LMWH during pregnancy did not include a placebo arm, since you can

	discuss whether it is ethical to ask women to inject themselves with placebo. These injections can be painful and might cause harm to the pregnant women. - The authors describe extensively what the possible role of LMWH on the development of the placenta could be. It is thought that the placenta is developed before 24 weeks gestation. How do the authors expect that the mechanism of action will be when the development of the placenta is already completed? - Exclusion criteria are, amongst others, use of LMWH or aspirin before enrollment of the trial. In the control variables history of preeclampsia is mentioned. One could expect that all women with a history of preeclampsia already use aspirin since it has been well investigated that is decreases a risk in a future pregnancy for recurrent preeclampsia (Bujold 2010, Askie 2007 etc.). - The authors refer to several studies regarding LMWH in pregnancy. However, I do miss the individualized patient data meta-analysis of Rodger et al (Lancet 2016) in which no beneficial effect was seen of LMWH in women with high risk pregnancies. This is one of the most recent publications regarding LMWH in pregnancy and has a high level of quality. I'm wondering if there is no effect in these high risk populations why the authors expect a beneficial effect in their lower risk population. - The definition IUGR is not completely clear to me and remains abstract: Intrauterine growth restriction (IUGR) is defined as a failure to achieve the endorsed growth potential secondary to placental insufficiency. Moreover, not al IUGR is related to placental insufficiency, but can also be related to congenital abnormalities etc. - In the section strengths and limitations of the study the authors mention that preterm IUGR affects a 0.5% of the pregnancies, however in the abstract and introduction 3% is mentioned. - Main outcome (prolongation of pregnancy) is in my opinion not a good primary outcome. We know that sometimes delivery is better for the fetus than prolongation of pregnancy, even if it is preterm. I would recommend to take the first mentioned secondary outcome; mortality and morbidity of the neonate, as primary outcome.

REVIEWER	Dr Katie Groom
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	This manuscript describes the trial protocol for a randomised controlled trial of low molecular weight heparin (LMWH), bemiparin, for the treatment of early onset intrauterine growth restriction (IUGR). This is an area of significant clinical interest for obstetricians and maternal fetal medicine specialists as there is currently no proven effective treatment other than delivery and its inherent risks. There have been a number of trials exploring the potential of LMWH for the prevention of placental mediated complications of pregnancy but none solely focused on IUGR and fewer, smaller trials exploring the potential of LWMH after the onset of IUGR for its treatment. This trial has been designed to assess the effect of LWMH on prolongation of pregnancy in cases of severe early onset disease but also includes outcomes that will provide additional information on the mechanisms of effect (if found to be effective). It is unique as all previous trials in pregnancy have not included a placebo group as comparator (standard care only, open label in previous trials). General comments:

	The dates of the trial and current status are not supplied and should be added. Reviewing Clinical trials.gov NCT03324139 it suggests recruitment commenced in October 2017. If already recruiting it is less appropriate for me to comment on trial design (and so have focussed on comments around strengthening the quality of the manuscript and minor elements of design). It seems likely the manuscript was not written by someone with English as first language and there are some areas where this is quite apparent. I would suggest the manuscript is reviewed and edited accordingly. For example but not limited to: page 5 lines 32-33 'To increase up to 10 times the blood supply during pregnancy these arteries become low resistance vessels', page 5 line 55' The natural history of placental insufficiency is towards the loss of fetal well-being' and page 14 line 40 'after fetal extraction'. There is inconsistent use of terms intrauterine growth restriction and fetal growth restriction. This should be amended to use one or other throughout the document. Title: This trial has been powered to assess the effect of LWMH on prolongation of pregnancy but the sample size includes only 50 patients and will not have sufficient power to demonstrate any effect on improved neonatal outcomes. I recommend that this should be reflected in the title with the inclusion of the word 'pilot' to describe the RCT as this trial will not conclusively demonstrate effect or be sufficient to change clinical practice. Abstract: This is adequate but I recommend modification of description for inclusion criteria as below. Strengths and limitations: Identifying that prolongation of pregnancy is only a surrogate marker of perinatal health is important, however, currently this statement suggests to me that prolongation of pregnancy will be a good thing. It is possible that additional time in-utero (in a hostile environment) may be detrimental, this could be commented on in the background section/discussion. Background: Appropriate summary of mechanisms by which LMWH may exert its effect. Summary statements of two meta-analyses of LMWH for prevention report positive effects. However, for a balanced opinion a further trial level meta-analysis and more recent IPD meta-analysis should also be included (Rodger MA, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. Blood. 2014;123(6):822-8 and Rodger MA, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet. 2016;388(10060):2629-41) with reference to the IPD concluding statement. Hypothesis and objectives: Inclusion of secondary hypotheses including angiogenic markers and placental examinations significantly strengthen this trial to allow exploration of mechanisms of effect (and would strengthen future larger RCTs). However, I note biomarkers are only to be collected at time of delivery (when presumably conditon has deteriorated and delivery is required or reached term gestation) – this may mean any significant effect, although unsustained may not be measured/recorded and no comparator for baseline collected. In addition the protocol suggets that only 2 biopsies of the placenta will be taken for RNA/DNA analysis – how will this acccuartely assess thrombotic and ischaemic lesions across the whole placenta? Trial design: This is not a phase IV trial (postmarketing surveillance/longer term/large numbers 1000+). This needs to be revised. Eligibility criteria: Table 1 suggests lower limit of gestational age is

	24 weeks, this should be included in list for inclusion criteria as well as upper limit. I recommend rewording of 'pulsatile'. This is not a term obstetricians are generally familiar with to describe umbilical artery and uterine artery Doppler – should this be pulsatile umbilical vein, notched uterine (uni or bilateral) or is it >95th percentile??? Exclusion cirteria includes prior aspirin use, the most high risk cases may be on aspirin early in pregnancy (past preeclampsia/IUGR). There is no clear reason for excluding these cases and will make results less generalisable. Control variables: Include information on preeclampsia and gestational hypertension in current pregnancy (not just history in previous pregnancy). Primary outcome: The hypothesis and power calculation is based on prolongation of pregnancy of one week and not absolute gestational age. Although randomisation is likely to equally distribute gestational age across both groups with such small numbers included and diverse gestational age range at inclusion (24-32 weeks) there may be some differnce in age at recrutiment (which may impact age at birth) and so the primary outcome should more clearly reflect the hypothesis i.e. prolongation of pregnancy not gestational age at birth. Secondary outcomes: Consider use of term 'birthweight' not 'neonatal weight'. Consider definition of preeclampsia used and move to new ISSHP definition (Editorial /Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 4 (2014) 97–104) or at least reference the definition proposed. Participant timeline: need to add maternal blood tests, cord bloods and placental sampling to table 1 (and consider additional time-points for maternal bloods – baseline and interim as noted above). Recommend some comment is included here about other standard care: frequency of USS, use of steroids/magnesium, indications for delivery (clinician led or directed by protocol). Trial safety: Note made of withdrawal criteria but I feel there should be specific section on trial safety in view of potential harmful effects of intervention. Withdrawal criteria should probably not be termed 'withdrawal' but 'indications to stop treatment early' (still in trial with intention to treat analysis). It seems there is no indication to stop treatment prior to delivery. If significant fetal compromise there is likely to be planned CS delivery. Will there be plan to stop treatment in advance for safety of regional anaesthesia and surgery? Data monitoring committee is commented on what about trial safety committee? Statistical analysis: Should be changed to prolongation of pregnancy not gestational age at birth (as noted previously). I acknowledge that there are limitations on number of levels of stratification at randomisation and adjustment in analysis with such small sample size, however, outcomes for A/REDF umbilical artery compared to positive end diastolic velocities are significantly different and unequal distribution across groups will have potential to significantly impact outcome of trial and should be considered/noted. Ethics and dissemination: Add NCT number as already registered. Recommend small discussion on the limitations of study – small sample size, will inform potential future larger trial, provide mechanistic data, prolonged pregnancy does not necessarily translate into better outcomes etc.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: David Petroff

General Comments
1. Primary outcome: please specify how the primary outcome is defined in the case of pregnancy loss, how will other missing data be treated
That is an interesting point that we missed. We will consider the occurrence of stillbirth a competing risk and we will perform a survival analysis to address such situation (R package cr17). Other missing will be treated as censored data.
Therneau T (2015). A Package for Survival Analysis in S. version 2.38, . Terry M. Therneau and Patricia M. Grambsch (2000). Modeling Survival Data: Extending the Cox Model. Springer, New York. ISBN 0-387-98784-3

2. I do not understand how the log-rank test of the primary objective will provide a meaningful additional analysis. The problem of pregnancy loss remains, though other causes of missing data may be treated as censored.
See our answer to our previous query.
The length of time from inclusion to delivery is not really a direct quantity of interest, it merely correlates very strongly with gestational age at birth.
We have already acknowledge that our main outcome is only a surrogate of perinatal heatlh. Many other trials in the field of perinatal medicine have used this surrogate (17pinPROM).
To account for the strong correlation between prolongation of pregnancy and gestational age, a Cox-regression analysis is planned, where gestational age at diagnosis will be treated as co-variate.

3. The power analysis contends that a “clinically relevant difference” in gestational age at delivery is 1 week although an earlier argument demonstrates that relevance depends strongly on current gestational week (“between 24 and 28 weeks, each week…increases survival without sequelae by 10-15%; and between 28 and 32 weeks…by 5%). Please provide the exact numbers for gestational age at birth from the “4 studies” in the meta-analysis, not just the differences.
We have added this information in the protocol.

4. It may not be possible to blind some personnel and patients effectively because of bruising. Please address this issue and perhaps collect data on blinding success within the trial.
We have added this issue in the BLINDING SUCCESS section in the mehods.
5. The primary outcome is not based on identical descriptions of methods between the registered trial (“caudal skull length”) and here (“crown rump length”). Please change the registered version accordingly.
We have already corrected this mistake.
6. A CONSORT checklist was provided, but in this context, I think a SPIRIT checklist would make more sense.
We have already provided a SPIRIT cheklist.

Specific comments
1. Abstract: The introduction is a little too long whereas the “Methods and Analysis” section presents nothing about the analysis. Please include information on the mathematical techniques to be used, treatment of missing data, etc.
We have added this information.

2. The section on “biological plausibility” is rather long compared to other parts of the manuscript.
We feel it is essential.

3. The section on “clinical evidence” is too one-sided for my taste. For one thing, the results of a large individual patients data meta-analysis (Rodger et al., Lancet, 2016; 388: 2629–41) should be

included, which included SGA as an outcome (Table 4) and the subgroup of women with previous SGA for a combined outcome (Table 5).
We have added this study.
For another, the statement that “these studies only include pregnant women at risk” seems to strong considering the studies from Yu et al quoted later (citations 19, 20) that do include many women with IUGR and have sample sizes larger than those planned here.
Compared to the series published by Yu et al., our study more specifically targets early IUGR (inclusión criterion <32 weeks) while in their studies the gestational age at delivery (around 37 weeks) suggesta a mixed early and late IUGR population.

4. The English is quite good, but should be looked over in some spots, e.g.
a. “endorsed” in Abstract
b. Typo “anlysis” in Abstract
c. “0.5% of pregnancies…has been shown to be effective” in Strengths and Limitations
d. “is only a surrogate” in Strengths and Limitations
e. “depends on the correct interaction” in Introduction
f. Lines 36-38 on page 5 “Fetal cytotrophoblast…spiral arteries”
g. Typo “discreet” as 6th control variable
h. “…allocation group from a web-based system” in ALLOCATION
i. “Patients will be informed that their participation…as their clinical documentation” (plural not singular) in ETHICS AND DISSEMINATION
j. “The trial has been entered in the public registry” in in ETHICS AND DISSEMINATION
We have corrected the English.

Reviewer: 2
Reviewer Name: Dr. C.N.H. Abheiden

There are several remarks I would like to make.
- It is a triple blind RCT and women are randomized to receive either LMWH or a placebo. All large trial investigating LMWH during pregnancy did not include a placebo arm, since you can discuss whether it is ethical to ask women to inject themselves with placebo. These injections can be painful and might cause harm to the pregnant women.
Our study protocol has been accepted by the local Ethics Committee (Clinical Research Ethics Committee (CEIC) of Sant Joan de Déu Hospital). In many other trials in perinatal medicine an injectable placebo has been used (17OH progsterone).

- The authors describe extensively what the possible role of LMWH on the development of the placenta could be. It is thought that the placenta is developed before 24 weeks gestation. How do the authors expect that the mechanism of action will be when the development of the placenta is already completed?
Effects of LMWH different from trophoblastic enhancement (among others, anti-inflamatory) are aready addressed in the background.

- Exclusion criteria are, amongst others, use of LMWH or aspirin before enrollment of the trial. In the control variables history of preeclampsia is mentioned. One could expect that all women with a history of preeclampsia already use aspirin since it has been well investigated that is decreases a risk in a future pregnancy for recurrent preeclampsia (Bujold 2010, Askie 2007 etc.).
We agree with this comment. We have modified our protocol to keep the patients with aspirin.

- The authors refer to several studies regarding LMWH in pregnancy. However, I do miss the individualized patient data meta-analysis of Rodger et al (Lancet 2016) in which no beneficial effect

was seen of LMWH in women with high risk pregnancies. This is one of the most recent publications regarding LMWH in pregnancy and has a high level of quality.
We have already added this study in the introduction.
I'm wondering if there is no effect in these high risk populations why the authors expect a beneficial effect in their lower risk population.
Our disease is incident IUGR, so it would be considered as high risk population.

- The definition IUGR is not completely clear to me and remains abstract: Intrauterine growth restriction (IUGR) is defined as a failure to achieve the endorsed growth potential secondary to placental insufficiency. Moreover, not al IUGR is related to placental insufficiency, but can also be related to congenital abnormalities etc.
In the methods section, a detailed definition of IUGR is given.
In the Delphi consensus, cases with abnormal karyotype are excluded. According to this, it is an exclusion creiterion of our study.

- In the section strengths and limitations of the study the authors mention that preterm IUGR affects a 0.5% of the pregnancies, however in the abstract and introduction 3% is mentioned.
We have corrected this sentences.

- Main outcome (prolongation of pregnancy) is in my opinion not a good primary outcome. We know that sometimes delivery is better for the fetus than prolongation of pregnancy, even if it is preterm. I would recommend to take the first mentioned secondary outcome; mortality and morbidity of the neonate, as primary outcome.

We aknowledge that our primary outcome is surrogate to perinatal health, however we would be largely underpowered if we set as a primary outcome neonatal mortality/morbidity.

Reviewer: 3
Reviewer Name: Dr Katie Groom
Institution and Country: University of Auckland, New Zealand
Please state any competing interests: none declared

It seems likely the manuscript was not written by someone with English as first language and there are some areas where this is quite apparent. I would suggest the manuscript is reviewed and edited accordingly. For example but not limited to: page 5 lines 32-33 'To increase up to 10 times the blood supply during pregnancy these arteries become low resistance vessels', page 5 line 55' The natural history of placental insufficiency is towards the loss of fetal well-being' and page 14 line 40 'after fetal extraction'.
We have reviewed the languade of the manuscript.

There is inconsistent use of terms intrauterine growth restriction and fetal growth restriction. This should be amended to use one or other throughout the document.
We have corrected this.

Title: This trial has been powered to assess the effect of LWMH on prolongation of pregnancy but the sample size includes only 50 patients and will not have sufficient power to demonstrate any effect on improved neonatal outcomes. I recommend that this should be reflected in the title with the inclusion of the word 'pilot' to describe the RCT as this trial will not conclusively demonstrate effect or be sufficient to change clinical practice.
We have included the Word "pilot" in the title.

Abstract: This is adequate but I recommend modification of description for inclusion criteria as below.

We have changed the inclusión criteria as suggested.

Strengths and limitations: Identifying that prolongation of pregnancy is only a surrogate marker of perinatal health is important, however, currently this statement suggests to me that prolongation of pregnancy will be a good thing. It is possible that additional time in-utero (in a hostile environment) may be detrimental, this could be commented on in the background section/discussion.
While prolongation of pregnancy is not in itself a direct measurement of benefit (additional time in-utero in a hostile environment may be detrimental) it coud be considered a desiderable outcome in managing this high-risk pregnancies, where gestational age at delivery has a marked impac on survival (Lees C et al. Ultrasound Obstet Gynecol. 2013 Oct;42(4):400-8).

Background: Appropriate summary of mechanisms by which LMWH may exert its effect. Summary statements of two meta-analyses of LMWH for prevention report positive effects. However, for a balanced opinion a further trial level meta-analysis and more recent IPD meta-analysis should also be included (Rodger MA, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. Blood. 2014;123(6):822-8 and Rodger MA, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet. 2016;388(10060):2629-41) with reference to the IPD concluding statement.
We have added these studies.

Hypothesis and objectives: Inclusion of secondary hypotheses including angiogenic markers and placental examinations significantly strengthen this trial to allow exploration of mechanisms of effect (and would strengthen future larger RCTs). However, I note biomarkers are only to be collected at time of delivery (when presumably conditon has deteriorated and delivery is required or reached term gestation) – this may mean any significant effect, although unsustained may not be measured/recorded and no comparator for baseline collected.
A baseline measurement at the time of diagnosis will be performed.
In addition the protocol suggets that only 2 biopsies of the placenta will be taken for RNA/DNA analysis – how will this acccuartely assess thrombotic and ischaemic lesions across the whole placenta?
We have added this information in the “collection and processing of placental tissue samples” of the methods.

Trial design: This is not a phase IV trial (postmarketing surveillance/longer term/large numbers 1000+). This needs to be revised.
We hace corrected this, phase III trial.

Eligibility criteria: Table 1 suggests lower limit of gestational age is 24 weeks, this should be included in list for inclusion criteria as well as upper limit. I recommend rewording of ‘pulsatile’. This is not a term obstetricians are generally familiar with to describe umbilical artery and uterine artery Doppler – should this be pulsatile umbilical vein, notched uterine (uni or bilateral) or is it >95th percentile???
We have already done these changes.

Exclusion cirteria includes prior aspirin use, the most high risk cases may be on aspirin early in pregnancy (past preeclampsia/IUGR). There is no clear reason for excluding these cases and will make results less generalisable.
We agree with it and then we have removed this exclusion criterion.

Control variables: Include information on preeclampsia and gestational hypertension in current pregnancy (not just history in previous pregnancy).
We have included it.

Primary outcome: The hypothesis and power calculation is based on prolongation of pregnancy of one week and not absolute gestational age. Although randomisation is likely to equally distribute gestational age across both groups with such small numbers included and diverse gestational age range at inclusion (24-32 weeks) there may be some differnce in age at recrutiment (which may impact age at birth) and so the primary outcome should more clearly reflect the hypothesis i.e. prolongation of pregnancy not gestational age at birth.
Following the reviewer comment, we have modified our randomizaion sequence stratifying for less and equal or more than 28 completed weeks.

Secondary outcomes: Consider use of term 'birthweight' not 'neonatal weight'.
We have changed it.
Consider definition of preeclampsia used and move to new ISSHP definition (Editorial /Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 4 (2014) 97–104) or at least reference the definition proposed.
We have used this definition recommended.

Participant timeline: need to add maternal blood tests, cord bloods and placental sampling to table 1 (and consider additional time-points for maternal bloods – baseline and interim as noted above).
Recommend some comment is included here about other standard care: frequency of USS, use of steroids/magnesium, indications for delivery (clinician led or directed by protocol).
We have added this changes recommended in table 1.

Trial safety: Note made of withdrawal criteria but I feel there should be specific section on trial safety in view of potential harmful effects of intervention.
We have added a section on trial safety as recommended.
Withdrawal criteria should probably not be termed 'withdrawal' but 'indications to stop treatment early' (still in trial with intention to treat analysis).
We have changed it.
It seems there is no indication to stop treatment prior to delivery. If significant fetal compromise there is likely to be planned CS delivery. Will there be plan to stop treatment in advance for safety of regional anaesthesia and surgery? Data monitoring committee is commented on what about trial safety committee?
For cases of elective CS treatment will stop 12 hours before. In cases of emergency CS, no stopping is planned.

Statistical analysis: Should be changed to prolongation of pregnancy not gestational age at birth (as noted previously).
We have modified it in the protocol.
I acknowledge that there are limitations on number of levels of stratification at randomisation and adjustment in analysis with such small sample size, however, outcomes for A/REDF umbilical artery compared to positive end diastolic velocities are significantly different and unequal distribution across groups will have potential to significantly impact outcome of trial and should be considered/noted.
We have added another stratification level according to absent/reverse or present end diastolic velocities in the umbilical artery Doppler.
Ethics and dissemination: Add NCT number as already registered.
We have added it.

Recommend small discussion on the limitations of study – small sample size, will inform potential future larger trial, provide mechanistic data, prolonged pregnancy does not necessarily translate into better outcomes etc.
We have added it.

VERSION 2 – REVIEW

REVIEWER	David Petroff, medical statistics
REVIEW RETURNED	31-Jan-2018

GENERAL COMMENTS	Mazarico and colleagues have addressed the points raised by the reviewers, though not always adequately in my opinion. As mentioned in my original review, I see it as our job to require that the trial be described with sufficient completeness, clarity and accuracy. This was already fulfilled in the original manuscript, so I continue to feel it can be published as is. Improvements to the design/manuscript that could still be made are as follows 1. Inclusion criteria: The third reviewer correctly noted that the inclusion criteria and Table 1 are not sufficiently precise. The diagnosis of early onset IUGR has to be made between the 20th and 32nd week. Does inclusion have to be within this time window? The last possible week for inclusion is crucial for the rationale that LMWH be effective. 2. Primary outcome: In their answer to my original question, the authors speak about treating missing data as censored and stillbirth as a competing risk. As far as I can see, this has not found its way into the manuscript. Instead, the use of multiple imputation is included for the treatment of missing data. One reason for this oversight may be that four analyses are foreseen for the “primary objective”. The interpretation of results would be much clearer if one analysis is treated as primary and the others, if at all, as sensitivity analyses. The use of imputation may well be appropriate for analyses I.A and II.A (gestational age as a continuous outcome), whereas censorship and competing risks could formally be used for survival analyses (I.B and II.B), though competing risks should be questioned. Stillbirth is perhaps a moot point and almost certainly a minor issue and could be relegated to the Statistical Analysis Plan. Missing data is likely to be a minor issue as well and imputation / censorship are acceptable, but the latter could be specified in the manuscript. The point that remains to my mind is that I stated in the original review that “the length of time from inclusion to delivery is not really a direct quantity of interest”. I am not criticizing the choice of gestational age as a surrogate. I am saying that by including women between the 20th and 32nd week (presumably what the authors intend), the Kaplan Meier curves are difficult to interpret and random differences between the groups regarding week at inclusion could lead to unwanted bias. This could be overcome by taking the 32nd week as the starting point and not randomization. Then, however, events before that week would present a problem. The origin of the difficulty is that these are not intrinsically time to event data – hence survival analysis is problematic. From the beginning of treatment, the question is not “how many weeks does the foetus remain in utero?”. For some 20 weeks would be ideal, for others 8. My recommendation: Choose method II.A for the primary analysis and discard the remaining three.

REVIEWER	Dr Katie Groom
REVIEW RETURNED	17-Jan-2018

GENERAL COMMENTS	Unfortunately not all of the changes have been highlighted or track changed and the original version was not available to cross-check against, however, the authors seem to have addressed the majority of issues raised in my first review. There are still a few English language issues and typographical errors but these are much improved (requires editorial review on level of acceptability). An example of this is the term 'after fetal extraction' - I would suggest 'after delivery (or birth) of the infant' would be a more suitable phrase. I still have some reservations about the primary outcome as 'gestational age at delivery'. The hypothesis relates to delay in delivery and the power calculation is made on prolongation of pregnancy and therefore I believe the primary outcome should be 'time from randomisation to delivery'. Other points to note - information on recruitment is included in data collection section. The intervention is planned to continue until delivery but only allows for maximum of 13 weeks but recruitment can be from 20 weeks. The background section remains very long and the detail about angiogenic markers seems excessive considering this is only a small part of the study. The discussion section is brief and could easily be elaborated on (with more relevance to readership than detail of markers etc).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: David Petroff, medical statistics
Institution and Country: Clinical Trial Centre, University of Leipzig, Germany
Please state any competing interests: None declared

Mazarico and colleagues have addressed the points raised by the reviewers, though not always adequately in my opinion. As mentioned in my original review, I see it as our job to require that the trial be described with sufficient completeness, clarity and accuracy. This was already fulfilled in the original manuscript, so I continue to feel it can be published as is.

1. Inclusion criteria: The third reviewer correctly noted that the inclusion criteria and Table 1 are not sufficiently precise. The diagnosis of early onset IUGR has to be made between the 20th and 32nd week. Does inclusion have to be within this time window? The last possible week for inclusion is crucial for the rationale that LMWH be effective.
The weeks for inclusion will be between 20 and 32 weeks of gestation, at the moment of diagnosis. We have already clarified this in the inclusion criteria.

2. Primary outcome: In their answer to my original question, the authors speak about treating missing data as censored and stillbirth as a competing risk. As far as I can see, this has not found its way into the manuscript. Instead, the use of multiple imputation is included for the treatment of missing data. One reason for this oversight may be that four analyses are foreseen for the “primary objective”. The interpretation of results would be much clearer if one analysis is treated as primary and the others, if at all, as sensitivity analyses. The use of imputation may well be appropriate for analyses I.A and II.A

(gestational age as a continuous outcome), whereas censorship and competing risks could formally be used for survival analyses (I.B and II.B), though competing risks should be questioned.
We have only left one primary outcome analysis (multiple regression of GA at birth and time from inclusion to live birth [recommended by reviewer 3]). As suggested by reviewer the reviewer we have discarded other analysis based on survival.
Stillbirth is perhaps a moot point and almost certainly a minor issue and could be relegated to the Statistical Analysis Plan. Missing data is likely to be a minor issue as well and imputation / censorship are acceptable, but the latter could be specified in the manuscript.
Both have been now specified in the manuscript. Following the reviewer´s recommendation we have discarded analysis based on survival. Stillbirth cases will be penalized in the analysis by imputing them to 0 days of prolongation.
The point that remains to my mind is that I stated in the original review that “the length of time from inclusion to delivery is not really a direct quantity of interest”. I am not criticizing the choice of gestational age as a surrogate. I am saying that by including women between the 20th and 32nd week (presumably what the authors intend), the Kaplan Meier curves are difficult to interpret and random differences between the groups regarding week at inclusion could lead to unwanted bias. This could be overcome by taking the 32nd week as the starting point and not randomization. Then, however, events before that week would present a problem. The origin of the difficulty is that these are not intrinsically time to event data – hence survival analysis is problematic. From the beginning of treatment, the question is not “how many weeks does the foetus remain in utero?”. For some 20 weeks would be ideal, for others 8.
My recommendation: Choose method II.A for the primary analysis and discard the remaining three.
Accordingly, we have only left one primary outcome analysis (multiple regression of GA at birth and prolongation of pregnancy [time from inclusion to live birth]).

Reviewer: 3
Reviewer Name: Dr Katie Groom
Institution and Country: University of Auckland, New Zealand
Please state any competing interests: None declared

Unfortunately not all of the changes have been highlighted or track changed and the original version was not available to cross-check against, however, the authors seem to have addressed the majority of issues raised in my first review.
1.- There are still a few English language issues and typographical errors but these are much improved (requires editorial review on level of acceptability). An example of this is the term 'after fetal extraction' - I would suggest 'after delivery (or birth) of the infant' would be a more suitable phrase.
The manuscript has been already reviewed by a professional scientific writing and editing service (BioScience writers).

2.- I still have some reservations about the primary outcome as 'gestational age at delivery’. The hypothesis relates to delay in delivery and the power calculation is made on prolongation of pregnancy and therefore I believe the primary outcome should be 'time from randomisation to delivery'.
We have now included only 2 primary outcome analysis: gestational age at delivery (as recommended by reviewer 1) and prolongation of pregnancy (as recommended by reviewer 3).

3.- Other points to note - information on recruitment is included in data collection section.
The intervention is planned to continue until delivery but only allows for maximum of 13 weeks but recruitment can be from 20 weeks.
It has been corrected. The maximum is 17 weeks.

The background section remains very long and the detail about angiogenic markers seems excessive considering this is only a small part of the study.
It has been summarized.

VERSION 3 – REVIEW

REVIEWER	David Petroff
REVIEW RETURNED	29-Mar-2018

GENERAL COMMENTS	The authors have addressed all the points raised. Thank you for the opportunity to review this manuscript and contribute toward improving the trial design. I wish the authors well for the trial and look forward to seeing the results.